

Low-Level Laser Therapy and Topical Medications for Treating Aphthous Ulcers: A Systematic Review

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Objective: The study compares low-level laser therapy with topical medications for treating aphthous ulcers.

Methods: A search of articles in this systematic review was completed in six databases. Treatment and comparative groups comprised of patients subjected to laser therapy and topical medications, respectively. Two different treatment outcomes were considered; pain and size of the lesion. Risk of bias was assessed using the Revised Cochrane risk-of-bias tool for randomized trials.

Results: From 109 articles, five randomized control trials fulfilled the selection criteria. The overall sample comprised of 98 males and 232 females, with a mean age of 32.4 years. The laser therapies in each included study had different active media and varying wavelengths. Topical medication used in the comparative group were triamcinolone acetonide, amlexanox, granofurin, and solcoseryl. Findings showed that patients who reported lower pain and decreased aphthous ulcer lesions were more in the laser therapy group than in the topical medication group.

Conclusion: Low-level laser therapy was better in treating aphthous ulcer lesions in comparison to topical medications, and all laser wavelengths in the included reports were seen to be effective. However, the results should be interpreted with caution, because no study demonstrated low-risk of bias in all the assessed domains.

Keywords: aphthous ulcer, recurrent aphthous stomatitis, low-level laser therapy, systematic review, evidence-based practice

Introduction

Aphthous ulcer (AU), also known as recurrent aphthous stomatitis (RAS), is a painful, benign, inflammatory lesion of the oral mucosa.¹ It is one of the most prevalent diseases in the oral cavity of adults,² and is reported to affect nearly 25% of them at least once in their lifetime.³ Amongst the three types; the smallest is the herpetiform ulcer, and the more prevalent is the minor aphthous or Mikulicz ulcer, which looks like an elongated lesion having a crateriform base, and is surrounded by a white-grey pseudo membrane. The third form is rare in comparison to the other two, and is called the major aphthous or the Sutton's ulcer.^{4,5} The experience of aphthous ulcer is painful, and may affect an individual's capacity to perform daily activities like eating and speaking.⁶ The pain exacerbates upon consumption of acidic foods or drinks, especially if the ulcers are near the throat or on the soft palate.² Maintaining good oral hygiene becomes an equally difficult task, and

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a recent study indicates the presence of commensal colonies of bacteria and other microorganisms in patients with aphthous ulcers. It further states that the oral microbiota of patients with aphthous ulcer is different from that of a healthy individual.⁷ With these it is evident that the presence of aphthous ulcers not only affects the oral health, but also hinders the daily performances, eventually impacting the oral health-related quality-of-life.⁸

Management and treatment of aphthous ulcers is challenging, as the etiology remains unclear.¹ Distinct treatment modalities such as anti-inflammatory drugs, anesthetics, immune modulators, antibiotics, and a few herbal therapies, are being prescribed.^{9,10} A review by Belenguer-Guallar et al¹⁰ compared pharmacological and non-pharmacological methods of managing recurrent aphthous stomatitis. The authors stated that the treatment usually starts with topical medications such as antiseptics, anti-inflammatory agents, analgesics, antibiotics, anesthetics, corticosteroids, and few natural substances. If there is no change in the signs and symptoms, then systemic therapy with antibiotics, corticosteroids, and immune modulators are preferred. However, systemic drugs produce side-effects, and, in some instances, the patients are forced to suspend the therapy.

More recently, lasers have been used in treating aphthous ulcers. Reports also compared and contrasted different types of lasers.¹¹ Among them, the low-level laser therapy is seen to produce analgesia, stimulate the healing process, and reduce the healing period.^{11–13} It is reported to be relatively safe with no clinical complications because of the low energy output,^{14,15} and the patients treated with low-level laser therapy were able to eat, drink, and brush their teeth normally just after 3 days of treatment.^{16,17} Though there are individual reports that demonstrate the benefits of using low-level laser therapy to treat aphthous ulcers, but they have not been appraised. Also, there is no substantial evidence to date that investigates the effectiveness of low-level laser therapy in comparison to topical medications. Thus, the current study aims to compare low-level laser therapy with topical medications for treating aphthous ulcers, and also to perform a qualitative assessment of the published reports.

Materials and Methods

Study Design

The current systematic review was planned and carried out between November 2019 and April 2020. The guidelines

provided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) were adopted so that substantial transparency is maintained in the selection process of the published reports.¹⁸

Research Question (PICO)

The following is the problem, intervention, comparison, and outcome (PICO) question addressed for the current study: “Is laser treatment more effective than the conventional topical medication in reducing the pain and size of aphthous ulcer lesions?” The disease or problem was the clinically diagnosed aphthous ulcer lesion. The intervention and comparison were laser therapy and topical medication, respectively. Two different outcomes, measured objectively (clinically) or subjectively (perceived), were pain and/or size of the lesion.

Eligibility Criteria

All the articles published to January 30, 2020, in English (as spoken and understood by all authors), irrespective of their study design (observational and experimental studies), were included. Moreover, studies that report lasers (with different wave lengths), and topical medications; benzalkonium chloride, choline salicylate, lignocaine, diclofenac, glucocorticoids, tetracycline, herbal medications, and/or combinations of any of these as a treatment option for aphthous ulcers were included in this review. Thoughtfully, the correspondences, commentaries, editorials, case reports, pilot studies, and animal studies were excluded as the quality of evidence provided by them is mostly weak.

Search Strategy and Data Extraction

The search process was completed independently by two investigators (MKA and MN), and any discrepancies in the lists of selected articles was intended to be cross-examined by another investigator (MFAQ) who was not involved in the search process. The electronic search of the published articles was conducted in the Web of Science (WoS), PubMed (Medline), Scopus, Embase, Cochrane, and Google Scholar databases. Keywords/Mesh-terms that were utilised in different combinations to obtain the relevant articles are reported in Table 1. A manual search of references from the included articles was additionally carried out. A data extraction chart provided online by Cochrane collaboration was used by two investigators (MFAQ and HG) to report on the author names, year of publication, study design, location/study setting, type of ulcer, treatment details, outcomes, side-effects, and time duration of follow-up (Table 2).

Table 1 Search Terms and Strategies

Search Strategy	Search Terms and Boolean Operators	Number of Articles Retrieved
#1	Aphthous ulcer OR aphthous stomatitis OR recurrent Aphthous stomatitis	
#2	Benzalkonium chloride	
#3	Choline salicylate	
#4	Lignocaine OR lidocaine	
#5	Diclofenac	
#6	Glucocorticoids	
#7	Tetracyclines	
#8	Laser*	
#9	Low level laser therapy (LLLT) OR photobiomodulation	
#7	#1 AND #8	83
#8	#1 AND #9	22
#9	#1 AND #2 AND #3 AND #4	1
#10	#1 AND #2	2
#11	#1 AND #3	3
#12	#1 AND #4	22
#13	#1 AND #5	0
#14	#1 AND #6	2
#15	#1 AND #7	1
	Total hits	136

Data Synthesis and Assessment of Risk of Bias

For the studies that were included, a narrative and tabular synthesis of data was carried out. The assessment of the risk of bias for the eligible studies was performed independently by two investigators (MFAQ and MFAQ), using the criteria provided by the Revised Cochrane risk-of-bias tool for randomized trials (RoB2).¹⁹ The domains for assessment included the risk of bias arising from; the randomization process (selection bias), deviations from the intended interventions (selection bias), missing outcome data (attrition bias), measurement of the outcome (detection bias), and selection of the reported result (reporting bias). The “low”, “some concerns”, or “high”, perceived judgments corresponded to the information

available from the published articles (Table 3). The agreement of scores from both the authors was assessed using the intra-class correlation coefficient (r).

Results

Study Identification and Screening

The search of articles from the aforementioned databases resulted in a total of 136 hits, which was consistent between the two independent search processes. About 27 duplicates were removed, and the remaining 109 articles were screened. From these, full texts of three articles were not available.^{20–22} Finally, five articles were eligible for data extraction and quality appraisals (Figure 1).

General Characteristics of the Included Studies

The overall mean age of the study participants from all five studies was 32.4 years; 98 were male, and 232 were female. The study settings with the increasing order of their date of publications were; Turkey in 2009,¹¹ Brazil in 2010,²³ Bulgaria in 2014,²⁴ India in 2016,²⁵ and Egypt in 2016.²⁶ The included studies were randomized clinical trials with a cumulative sample of 330 (N), of which 155 patients were treated with laser therapy, 145 with topical medications, 15 underwent a placebo treatment, and the remaining 15 were treated with herbal medications.

Description of Laser and Topical Treatments

The laser therapies in each of the included studies had different active media. For instance, the therapy with diode lasers used a semiconductor diode as an active medium, the Nd:YAG laser had neodymium-doped (Nd) yttrium aluminium garnet (YAG) crystals, and the InGaAlP laser had aluminium gallium arsenide as the active medium. Subsequently, the dosage for laser therapy in the treatment groups and the topical medication in the comparative groups were also distinct (Table 2). Tezel et al¹¹ used a Nd:YAG laser with a wavelength of 1.064 nm and compared it with triamcinolone acetonide, while De Souza et al²³ used an InGaAlP diode laser with 670 nm and compared it to triamcinolone acetonide. Jijin et al²⁵ used an AMD laser (810 nm) compared with Amlexanox. Nasry et al²⁶ used a diode laser (970 nm), comparing it with a herbal paste and Amlexanox, and, finally, Lalabonova and Daskalov²⁴ used a diode laser with different wavelengths (658 nm) and compared it with

Table 2 Description on Study Setting, Sample, Exposure, Outcome, and Conclusion of the Included Studies

Item	Author, Year	Study Setting	Sample Description	Laser Treatment	Topical Medication	Follow Up	Conclusion (Healing Time, Pain, Size of Ulcer, Reoccurrence)
1	Tezel et al, 2009 ¹¹	Turkey	Total sample: n=20 Male=7 Female=13 Laser group: n=10 Male=3 Female=7 Topical medication group: n=10 Male=4 Female=6	Anesthetic Gel (articaine 4%) + Nd: YAG laser 1.064 nm Dose: Under air-cooling with 2–3 minutes duration.	Triamcinolone Acetonide. Dose: Three times daily for 1 week.	Days 1, 4, and 7	Pain: Laser – immediate pain relief and faster healing Topical medication group - gradual reduction on day 5. Patient preference: Significant in Laser group Post-treatment complications (chewing, speaking lower in Laser group) Erythema – no difference in both groups.
2	De Souza et al, 2010 ²³	Brazil	Total sample: n=20 Male=8 Female=12 Laser group: n=15 Topical medication group: n=5 Age: up to 70 years	InGaAlP diode laser, 670 nm. Dose: 1 minute, laser pen touching the surface of lesion.	Triamcinolone acetonide administered four times daily, as long as lesion persisted.	Day 1 to day 7	Pain: 86.6% of the patients, having undergone laser treatment, reported a reduction in pain in the same session ($P=0.0006$). Regression time: No significant difference observed between the two groups.
3	Lalabonova and Daskalov., 2014 ²⁴	Bulgaria	Total sample: n=180 Male=31 Female=149 Mean age: 43.01 (1.05) years	SIX Laser TS diode laser – 658 nm. Dose: One session a day until symptoms abated.	Granofurin and Solcoseryl. Dose: Twice daily until symptoms disappeared.	Days 1, 2, 3, and 5	Pain: Laser group: Day 3=100% patients pain free Topical medication group: Day 5=44.4% pain free Erythema: Laser group: Day 3=100% patients with no erythema Topical medication group Day 5=22.3% patients with no erythema Epithelization: Laser group: Day 5=75.6% of patients with complete epithelization. Topical medication group: Day 5=37.8% patients with complete epithelization.

(Continued)

Table 2 (Continued).

Item	Author, Year	Study Setting	Sample Description	Laser Treatment	Topical Medication	Follow Up	Conclusion (Healing Time, Pain, Size of Ulcer, Reoccurrence)
4	Jijin et al, 2016 ²⁵	India	Total sample: n=50 Male=29 Female=21 Laser group: n=25 Male=14 Female=11 Topical medication group: n=25 Male=15 Female=10 Age: 15–55 years	AMD laser 810 nm Dose: 30 seconds, and 3 times with 2 minute interval. Applied twice after day 1 day of treatment, followed by day 3 and day 7.	5% Amlexanox given four times daily for 7 days.	Days 1, 3, and 7	Pain: The mean pain score was significantly less in the laser group on day 3 than the Amlexanox group, but not by day 7.
5	Nasry et al, 2016 ²⁶	Egypt	Total sample: n=60 Male=23 Female=37 Age: 19–40 years	Group III: Diode laser, 970 nm Dose: 30–45 seconds with 15–20 seconds gap, 4 sessions. I, II, IV – applied 4 times, 5 days.	Group I: Herbal paste combination (Glycyrrhiza glabra + Acacia nilotica) Group II: Amlexanox Tabs (2 mg) Group IV: Placebo adhesive tablets.	Immediately, and on days 2 and 5	Pain and size: Group III – Laser group reported highest reduction in pain and ulcer size on day 5. Group I showed reduction in pain and size when compared to control group IV.

Granofurin and Solcoseryl (Table 2). However, none of the included studies had reported plausible side-effects in the treatment or the comparative groups.

Comparative Findings of Laser Therapy and Topical Medications

The overall results showed that patients who reported lower pain and decreased aphthous ulcer lesions were more in the laser therapy group than in the topical medication group, at the end of a specified follow-up period in each of the included studies. This suggests that laser therapy was effective in reducing the pain and size of the lesions, compared to topical medications (Table 2). In general, the follow-up period was up to 7 days, except in

the study performed by Lalabanov et al,²⁴ where it was 5 days. Tezel et al¹¹ and Jijin et al²⁵ reported their results for days 1, 4, and 7, and days 1, 3, and 7, respectively. De Souza et al²³ examined the outcomes for each day, from day 1 to 7, and provided a cumulative result in favor of laser therapy. Finally, in the study by Nasry et al,²⁶ the laser group showed a decrease in pain and size of ulcer when checked on day 2 and 5.

Risk of Bias

The risk of bias was reported using the criteria provided by Revised Cochrane risk-of-bias tool for randomized trials (RoB2).¹⁹ The assessment was undertaken by two independent reviewers, and the risk of bias judgments for each

Table 3 Risk of Bias Assessment Using the Cochrane Guidelines (RoB-2)

Item	Signaling Question	Tezel et al, 2009 ¹¹	Lalabonova and Daskalov 2014 ²³	De Souza et al, 2010 ²⁴	Jijin et al, 2016 ²⁵	Nasry et al, 2016 ²⁶
Domain 1: Risk of bias arising from the randomization process (selection bias)						
1.1	Was the allocation sequence random?	Yes	No	No	No	No
1.2	Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No	No	No	No	No
1.3	Did baseline differences between intervention groups suggest a problem with the randomization process?	No	No	No	No	No
Risk of bias judgment		Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Domain 2: Risk of bias due to deviations from the intended interventions (selection bias)						
2.1	Were participants aware of their assigned intervention during the trial?	Yes	Yes	Yes	Yes	Yes
2.2	Were people delivering the interventions aware of participants' assigned intervention during the trial?	Yes	Yes	Yes	Yes	Yes
2.3	Were there deviations from the intended intervention that arose because of the trial context?	No	No	No	No	No
2.4	Were these deviations likely to have affected the outcome?	N/A	N/A	N/A	N/A	N/A
Risk of bias judgment		Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Domain 3: Risk of bias due to missing outcome data (attrition bias)						
3.1	Were data for this outcome available for all, or nearly all, participants randomized?	Yes	Yes	Yes	Yes	Yes
3.2	Is there evidence that the result was not biased by missing outcome data?	N/A	N/A	N/A	N/A	N/A
3.3	Could missingness in the outcome depend on its true value?	N/A	N/A	N/A	N/A	N/A
3.4	Is it likely that missingness in the outcome depended on its true value?	N/A	N/A	N/A	N/A	N/A
Risk of bias judgment		Low risk	Low risk	Low risk	Low risk	Low risk
Domain 4: Risk of bias in measurement of the outcome (detection bias)						
4.1	Was the method of measuring the outcome inappropriate?	No	No	No	No	No
4.2	Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No	No	No	No
4.3	Were outcome assessors aware of the intervention received by study participants?	Yes	Yes	Yes	Yes	No
4.4	Could assessment of the outcome have been influenced by knowledge of intervention received?	Yes	Yes	Yes	Yes	No
Risk of bias judgment		High risk	High risk	High risk	High risk	Low risk

(Continued)

Table 3 (Continued).

Item	Signaling Question	Tezel et al, 2009 ¹¹	Lalabonova and Daskalov 2014 ²³	De Souza et al, 2010 ²⁴	Jijin et al, 2016 ²⁵	Nasry et al, 2016 ²⁶
Domain 5: Risk of bias in selection of the reported result (reporting bias)						
5.1	Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes	Yes	Yes	Yes	Yes
5.2	Multiple eligible outcome measurements (eg scales, definitions, time points) within the outcome domain?	Yes	Yes	Yes	Yes	Yes
5.3	Multiple eligible analyses of the data?	No	No	No	No	No
Risk of bias judgment		Low risk	Low risk	Low risk	Low risk	Low risk

Notes: Data from Sterne et al.¹⁹

domain were almost identical (overall, $r=0.91$); the minor discrepancies were sought by mutual consensus. The final judgments on the risk of bias for all five studies are presented in Table 3. Even though the studies had stated the use of randomization, they did not provide any description on the process, except for Tezel et al.¹¹ Most studies had “some concerns” in the allocation bias domain. There was no missing data in any of the included studies; and only the study performed by Nasry et al had the outcomes assessed by blinded clinicians.²⁶ Therefore, none of the included studies could be considered to be of high quality.

Discussion

Aphthous ulcer has an uncertain etiology, and, consequently, there is no definitive treatment.²⁶ Numerous studies have been carried out to find the best and most effective treatment regime. Most treatments targeted pain reduction, decrease in size of the lesion, and inhibition of reoccurrence. The current review was carried out to determine if laser treatment was better than topical medication in addressing one or more of these treatment outcomes. The findings from the clinical trials included in this review unequivocally demonstrated that laser therapy was better than topical medications in relieving pain and decreasing its size.

Data on the use of laser therapy for aphthous ulcer is not extensive, and only a few studies have compared the effectiveness of laser therapy with other pharmacological treatments.²⁷ Those studies had reported concurrent findings. It was observed that patients with aphthous ulcers had better tolerance for laser therapy (Nd:YAG) than topical

corticosteroids (triamcinolone acetonide).^{11,28} In addition, the ulcers reappeared after treatment with topical corticosteroids, in contrast to no recurrence after laser therapy; and both groups were subjected to a constant follow-up period.²⁸ De Souza et al,²³ in 2010, reported immediate pain reduction and faster healing in patients treated with laser therapy, compared to the group treated with triamcinolone acetonide. Nearly 90% of patients exposed to laser treatment in the study performed by Lalabonova and Daskalov²⁴ were relieved from pain and erythema on the second day, whereas 55% of the patients in the topical ointment group (Granofurin and solcoseryl) reported pain until day 5 of the treatment. However, in the study by Jijin et al²⁵ intergroup comparison to assess the size of the lesion demonstrated non-significant findings, and the medication group had received 5% Amlexanox oral paste.

Only one study to date has compared three treatment categories, which included herbal paste (*Glycyrrhiza glabra* and *Acacia nilotica*), conventional medication (Amlexanox 5%), and laser irradiation.²⁶ Study participants reported lower pain scores and demonstrated better reduction in the ulcer size in the Amlexanox and Laser groups, compared to the herbal paste group. Amongst all, the laser group showed a higher proportion of patients with lower pain scores and reduced ulcer size.²⁶ This effective result of Amlexanox 5% was also shown in another study where it was compared with a combination of benzalkonium chloride, choline salicylate, and lignocaine. Although the patients in both groups showed a significant reduction in the number, size, and ulcer pain when compared to the baseline recordings, patients treated

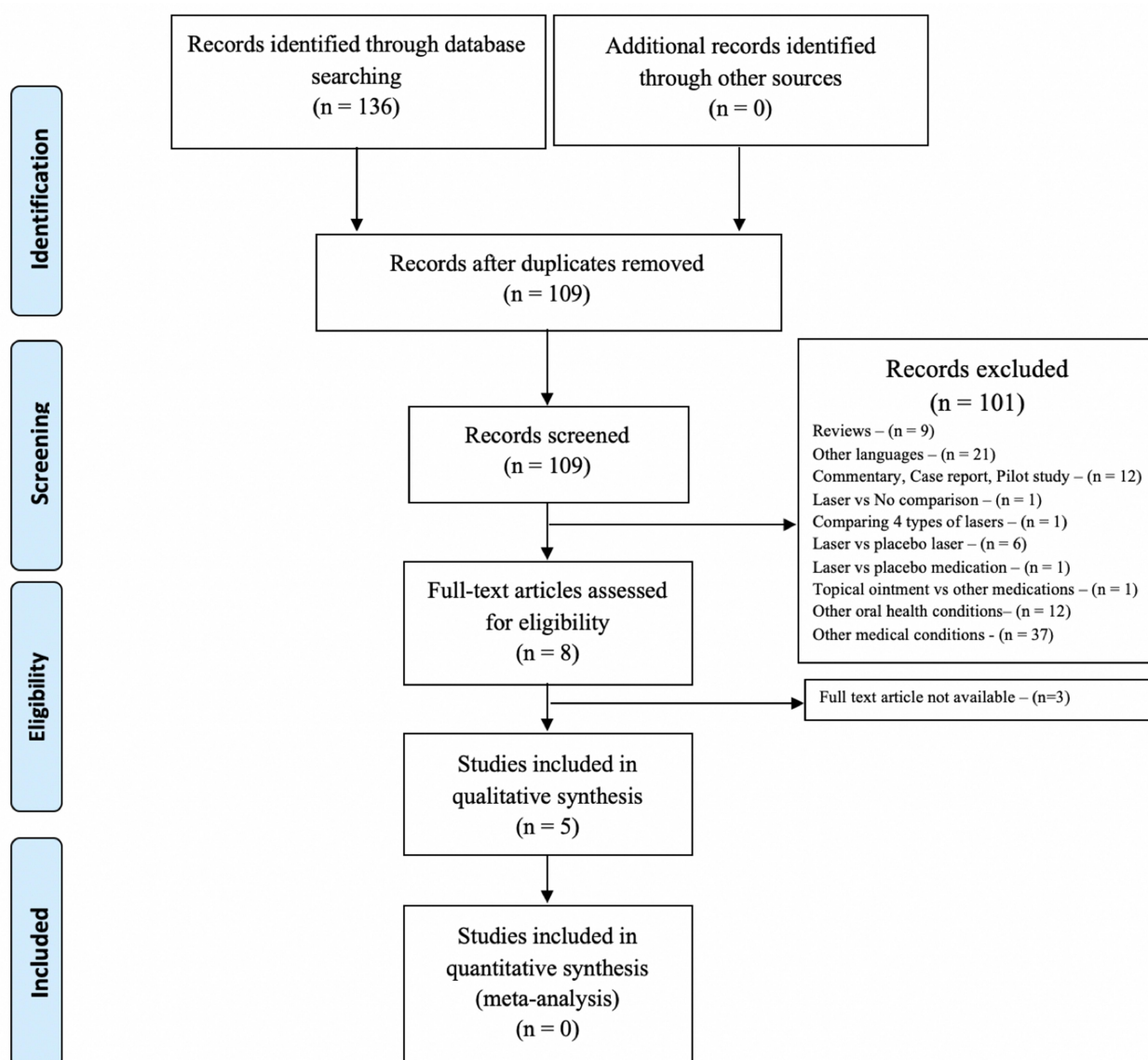


Figure 1 PRISMA flow chart illustrating the study selection process.

Notes: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*. 2009;62(10). Creative Commons.

with Amlexanox 5% showed a significant difference between the groups.²⁹

The effective dose of laser in each of the studies was different and dependent on the type of laser utilized. Rocca et al,³⁰ upon comparing the wavelengths (Er:YAG, Diode lasers – 450 nm, 635 nm, 808 nm) had shown that a wavelength of 635 nm was more effective in relieving pain. In addition, where lidocaine was applied before the laser therapy, the pain reduction was more substantial.³¹ In order to judge the healing time, two studies matched placebo laser therapy with CO₂ laser therapy and indicated

that the healing time was much shorter in patients treated with CO₂ therapy,^{12,13} however, another study performed by Sattayut et al³² reported no significant difference in the healing time and pain level between the CO₂ laser and placebo groups. Thus, a substantial evidence on the dose of lasers is warranted, and eventually the difference in the type and dose of lasers in each included study did not facilitate the meta-analysis of the numerical data.

Further, multivitamins are prescribed along with laser therapy; however, the evidence supporting their use is ambiguous. With the assumption that aphthous

ulcer lesions are related to vitamin B 12 deficiency, a randomized double blind placebo-controlled trial was carried out by Volkov et al³³ and, after 4 months of treatment, it was observed that vitamin B12 supplements were effective. In accordance to this, Yasui et al³⁴ also suggested the use of Vitamin C in treating minor aphthous ulcers. Furthermore, studies have also reviewed the use of omega 3 (1,000 mg) for minor aphthous ulcers, and reported a reduction in the ulcer duration and pain scores.^{35,36} On the contrary, some studies disagree with the use of multivitamins, as no significant difference was observed upon its comparison to a placebo effect.^{37,38} Accordingly, Lalla et al³⁷ suggested not to prescribe multivitamins on a routine basis to treat aphthous ulcers. Nevertheless, there are studies that recommend preclinical examinations of R.B.C count, vitamin B12 levels, and levels of folic acid in the body, as their deficiency may inhibit the effectiveness of the therapy.^{39–41}

To the best of our knowledge, this is the first systematic review undertaken to compare the effectiveness of laser therapy and topical medications in the treatment of aphthous ulcers. The earlier literature review by Vale (2015) had concurrent findings, but did not include reports from at least three studies.^{11,23,24} Next, the reviews by Najeeb et al²⁷, and Han et al⁴² stated the effectiveness of low-level laser therapy, but did not intend to compare it with topical medications. These results, although similar, were not suitable to compare and contrast with the findings from the current systematic review due to evident reasons. The risk of bias assessment was also an important aspect of this review, as it provided the scores for the quality of research conducted. Although the results show that laser therapy was better in reducing the pain and size of the lesion, the results should be interpreted in accordance with the limitations of the studies included in the review. The risk of bias assessment judgment inferred that most of the studies did not describe how the randomization process was conducted. In addition, four out of five studies did not have a blinded investigator to assess the outcome. Cochrane guidelines state that each step in the methodology should be clearly explained to achieve a low risk score in the five domains of assessment. Therefore, further evidence using robust methodologies is warranted to substantiate the effectiveness of laser therapy over other treatment approaches. Also, the randomized control trials should consider reporting the potential side-effects that are experienced by the patients while undergoing laser therapies and/

or treatment by medication. Finally, it is highly recommended that a general clinical protocol be derived for the use of laser therapy in treating aphthous ulcer lesions.

Conclusion

In conclusion, low-level laser therapy was better in treating aphthous ulcer lesions in comparison to topical medications, and all laser wavelengths in the included reports were seen to be effective. However, the results should be interpreted with caution, because none of the included studies demonstrated a low-risk of bias in all the assessed domains.

Knowledge Transfer Statement

The current study provides an insight to the clinicians on the treatment of aphthous ulcers by comparing low-level laser therapy with the commonly prescribed topical medications. It is observed that the patients who reported lower pain and decreased aphthous ulcer lesions were more in the laser therapy group than in the topical medication group.

Author Contributions

All authors contributed to design, implement, and draft or revise the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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The authors of the current review do not have any competing interests to declare.

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